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THE TOLERANCE DOSE

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THE TOLERANCE DOSE

By S. T. Cantril, M. D. and H. M. Parker

DEFINITION OF TERMS

In the development of the science of radiotherapy, a special nomenclature has grown up, which, for the most part, is clear and unambiguous to the doctors and physicists engaged in the field. For special reasons, some of the quantities involved were defined in a different manner from that in which analogous quantities in pure physics would have been handled. The present project makes it a matter of general interest to correlate these two aspects. Some account of the terms used will therefore be given before proceeding to the main discussion.

Dose

Webster defines dose as: (a) The measured quantity of a medicine to be taken at one time or in a given period of time. (b) A definite quantity of anything regarded as having a beneficial influence. (c) Anything nauseous that one is obliged to take.

The radiotherapist presumably accepts definition (b) in considering the radiation effect on his patients, and definition (c) in considering the effect upon himself.

Webster's definitions are based on the simple picture of the swallowing or injection of a measured quantity of material. With rare exceptions, such a quantity is retained by the body for a period long in comparison with the giving of the dose. The radiation case is quite different. When the body is subjected to X radiation or gamma radiation, some part of the incident energy is converted into kinetic energy of secondary electrons. In general, the major part of the incident energy is transmitted without interaction. It is assumed that the tissue is affected only by the energy absorbed. Dose, in the sense used in radiotherapy, refers then to the energy absorbed in the tissue. In principle, dose could be measured directly in terms of energy absorption per unit volume, but the practical difficulties are great, and it is better to determine dose indirectly by ionization measurements under certain prescribed conditions.

The Roentgen

The principles of dosimetry indicate that the ionization per unit volume arising in a sufficiently small cavity in an absorbing medium subjected to X or gamma irradiation is approximately proportional to the energy absorbed per unit volume in the medium at the same point. Although this relation would in itself provide a feasible method of dosimetry, it was avoided in the setting up of international standards because it requires the use of an ionization chamber with "tissue-walls." No general agreement about such a tissue wall could be reached. It was, therefore, decided to use the ionization inside and air-wall or air-equivalent wall cavity as the standard of reference. In this system the unit dose, called the roentgen was the quantity of X or gamma radiation that liberated 1 esu of charge per unit volume of standard air in such a hypothetical air-wall ionization chamber.

The merit of the system was that over the range of wavelength used in radiotherapy, the energy absorbed per gram of soft tissue was sufficiently accurately the same as that absorbed per gram of air.

The correlation broke down when the biological material concerned was either skin, which contains enough sulphur to give an important photoelectric contribution, or bone, in which the air-walled cavity gives an entirely erroneous picture of the energy absorption. With these exceptions, it became common practice to state that the roentgen corresponds to an energy absorption of 83 ergs per gram of tissue or to the production of 1.61×10^{12} ion pairs per gram of tissue.

When neutron therapy began to be used, the air-wall chamber method of measurement broke down. It was relatively easy to make an air-equivalent material with respect to X or gamma rays since this depended only on the electron density and the artificial matching of the photoelectric effect over a wide enough range. For fast neutron irradiation, the hydrogen content of the chamber wall became the prime factor. So far the tentative methods of neutron dosimetry have used the following devices:

a) A pure carbon wall, chosen because of its reproducibility (L. H. Gray).

b) The Bakelite wall, coated with Aquadag, of the customary 100 r Victoreen condenser r-meter (the n unit of P. Aebersold).

c) Pure water (presumably as ice?). Another generally available substance, but this time with approximately the correct amount of hydrogen (L. H. Gray).

d) Basic dosimetry with different walls and chamber gases to deduce the tissue-equivalent dose (L. H. Gray).

e) Paraffin wall with ethylene gas. (E. O. Wollan).

f) The balanced double ionization chambers filled respectively with argon and a gas rich in hydrogen (Wollan, Gamertsfelder, Parker).

In the meantime, many writers have extended the roentgen as an abbreviation for 83 ergs per gram of tissue of 1.61×10^{12} ion pairs per gram to include neutron irradiation, beta radiation, and any radiation that produces ionization in tissue. This unit has been variously specified as the "tissue-roentgen," which restricts to tissue a device usefully applied to water, polystyrene, etc., as the "roentgen-equivalent" or "equivalent-roentgen," which is misleading because the biological effect is certainly not equivalent and as the "e" was used in Europe for a unit similar to, but not identical with the "r." The present writers prefer to use the expression "roentgen equivalent physical" (rep) for the time being. If such a unit ultimately proved to have any advantage over the direct statement of energy absorption in ergs per gram, it might be a more suitable vehicle for the honoring of the name Bragg than of Roentgen, since it depends on the Bragg principle of dosimetry. Frequently there is no confusion in writing "roentgen" instead of "rep" when the latter is clearly implied.

"Rem"

Another concept enters into the discussion when tolerance dose is considered in relation to varying radiations. This is the variation in effect upon similar tissues produced by an equivalent energy absorption of different types of incident radiation, i.e., alpha, beta, gamma, fast neutrons, etc. Thus, there has been formed the concept of a "biologically equivalent roentgen," namely a quantity of energy absorbed which produces an equivalent effect regardless of the character of the incident radiation. The logical term to express this concept is "roentgen equivalent biological," abbreviated "reb." This, in speech, can be so easily confused with "rep," that we have in use adopted the abbreviation "rem" which can be understood to imply "roentgen equivalent man, mouse, or mammal," depending upon the biological effect under discussion.

Dosage Rate

By convention, dose per unit time is called <u>dosage rate</u>. Some writers prefer dose rate. There is an alternative expression using <u>exposure</u> instead of <u>dose</u>, and exposure rate instead of dosage rate. The essential point is to distinguish between <u>dosage rate</u> and intensity. The former is essentially a measure

of energy absorption per unit time, the latter is the energy flux. The relation between dosage rate and intensity is therefore a function of the absorbability of the radiation in question. The more recent radiological literature has carefully observed this distinction, but the older papers frequently expressed intensity in terms of r per unit time.

Tolerance Dose

Webster has "tolerance" invariably a noun, the possible relevant meanings being (a) the act of tolerating, quality of being tolerant, or (b) constitutional or acquired capacity to endure a shock or poison, etc.

Some objectors to the double noun use "toleration dose," an equally formidable double noun. Presumably, "tolerable dose" was originally intended. "Permissible exposure" would be a suitable name in the exposure nomenclature. For the present purposes, tolerance dose will be assumed to be that dose to which the body can be subjected without the production of harmful effects. It is not self-evident whether dose as used here refers to a total dose or to the elements of dose in a given period of time. This will be discussed later. The present writers will take the latter view and further specify that the given period of time shall be one day.

Tolerance Dosage Rate

Tolerance dosage rate has to be interpreted as the dosage rate that is continuously tolerable. The present writers will say that the daily tolerance dose is 0.1 r (in general). If one writes "the tolerance dose is 0.1 r per day," it is argued that this expression is dimensionally a dosage rate, and that one should write "the tolerance dosage rate is 0.1 r per day." There is here a difference in attitude which can be resolved only by a resumé of the manner in which tolerance dose has come into the literature. (Editor's note: Since this was written, the term "maximum allowable exposure" has been temporarily agreed to as the most acceptable term for "tolerance dose.")

Tolerance Dose Versus Tolerance Dosage Rate

The question of interpretation between dose and dosage rate ultimately leads to far-reaching differences of opinion concerning the permissible exposure of the body. The origin of the difficulty is closely related to the development of radiotherapy since 1928. The current International Recommendations for X-Ray and Radium Protection read as follows:

"The evidence at present available appears to suggest that under satisfactory working conditions, a person in normal health can tolerate exposure to X rays or radium gamma rays to an extent of about 0.2 international roentgen per day or 1 r per week. On the basis of continuous irradiation during a working day of seven hours, this figure corresponds to a tolerance dosage rate of 10^{-5} r per second."

It is clear that the persons responsible for these recommendations had in mind that it was immaterial whether the exposure was taken in equal daily amounts or whether it was averaged over a week. The earlier writers frequently quoted the permissible exposure per month. In all this, there was no restriction on the doasge rate other than the implication that the exposures received were such as would normally arise in X-ray or radium work. The crux of the problem is, then, the normal mode of receiving unwanted radiation. This occurred in four principal ways:

1) Fluoroscopists— The fluoroscopist was exposed to short bursts of quite intense radiation (of the order of 10^{-1} r/sec on the hands and 10^{-3} r/sec on the body).

2) X-Ray Therapy Technicians—In this case the technician was exposed to radiation for periods of about 5 to 30 minutes with intervals of the same order between treatments. Before the advent of self-protected tubes and special shielding, a typical dosage rate for these exposures would be 10^{-4} r/sec. At the present time, the exposure of X-ray technicians is so little that, in general, it adds nothing to our knowledge of tolerance.

3) X-Ray Therapy Patients—It is debatable whether patients should be included because their exposure is received over a period of weeks rather than years. However, in therapy, a large portion of the body receives a dose of the order of 1 per cent of that delivered to the treated part. Since it would not be uncommon to deliver 4000 r to each of two or three fields, the body can receive 80 to 120 r in a few weeks, at a dosage rate of about 10^{-2} r/sec. Such an irradiation is not without demonstrable effects, but it is believed to cause no permanent damage. A dose of this magnitude is a three-year quota of daily tolerance doses. A study of patients subjected to repeated courses of X-ray treatment would be instructive except that most of the patients so treated would die too quickly of other causes.

4) Radium Therapists and Technicians—These men were exposed for periods up to one hour at irregular intervals, with a background of perhaps 2 x 10^{-6} r/sec through the working day. The highest dosage rate normally encountered would be about 10^{-3} r/sec.

In all cases it appears that the exposures from which the present knowledge of tolerance was derived were given in relatively short bursts at dosage rates mainly in the range of 10^{-4} to 10^{-3} r/sec. This should be sufficient evidence that no special significance should be attached to a tolerance dosage rate of 10^{-5} r/sec. The inclusion of this figure in the International Recommendations was, we believe, nothing more than a recognition of its convenience as a guide when protection measurements are made with a survey meter, calibrated in r/sec. All points at which the dosage rate is permanently less than 10^{-5} r/sec can be considered safe.

On the whole, the exposure of personnel regularly employed in a radiation-hazardous occupation will be more or less evenly distributed except for week-ends.* In addition, a large body of information on repeated daily exposures of patients has been built up. For these reasons, the authors propose to restrict the meaning of tolerance dose to daily tolerance dose. This procedure is somewhat arbitrary. There is nothing magic about a period of one day, and we would manifestly be in an absurd position to claim that 0.1 r can be delivered daily with any time distribution in the day, and that 0.2 r cannot be given every alternate day or 0.5 r or 0.6 r every working week. Nevertheless, there has to be some limit to the dose-time relation, and the daily limit is convenient. No restriction need be placed on the dosage rate at which the daily general body radiation is received. Conditions should not exist in which the body can receive the daily quota of 0.1 r in less than 10 seconds, and this automatically limits the maximum dosage rate to about 10^{-2} r/sec which differs by only a factor of 10 from the dosage rates giving rise to our general knowledge of tolerance.

Statement of Tolerance Dose Levels

The tolerance dose levels which we have accepted as a working basis and which will be discussed in more detail are:

X and gamma radiation	0.1 r per day
Beta radiation (external)	0.1 rep per day
Fast neutron radiation	0.025 rep per day
Radon concentration in working rooms	1 x 10^{-14} curie/cc
Radium deposited in the body	0.1 microgram

*However, radium technicians in the larger institutions are frequently "on radium" and "off radium" in alternate months. It is fairly well established that freedom from radiation for four weeks gives the blood a chance to recover from potential damage.

THE HISTORY OF THE TOLERANCE DOSE

A severe case of X-ray dermatitis was described in July 1896, only a few months after the discovery of X rays. It was not until 1902 that Rollins[1] attempted to formulate some idea of a tolerance dose. He suggested that "if a photographic plate is not fogged in seven minutes, the radiation is not of harmful intensity." In present day terminology this would amount to perhaps 10 to 20 r per day delivered by soft X rays. The early injuries of radiation were largely those of the skin, but the demonstration of the marked radiosensitivity of the blood forming organs (1904–1905) and of the reproductive organs of animals (1903–1904) carried some warning that more serious damage than dermatitis could be anticipated. The first organized step to insure protection from X rays was made in 1915 by Russ,[2] who read a paper on protective devices before the British Roentgen Society.

"Because of the war activity which existed then, this plan failed to bring forth important advancement. As a result of war demands, caution gave way to action and protective measures were again forgotten. Taking increased risks at this time probably was a factor which contributed to an unfortunate development in 1919 and 1921, both in this country and in Europe, when a number of prominent radiation workers died of apparent radiation injuries, particularly aplastic anemia. Unfavorable publicity developed, and definite action resulted."

The American Roentgen Ray Society formed a committee in 1920 to recommend protection measures, which were formulated and published in September 1922. The British X-Ray and Radium Protection Committee presented its first recommendation in July of 1921. The two sets of recommendations were quite similar and dealt largely with protective materials recommended for use in building X-ray and radium laboratories and apparatus.

At the first International Congress of Radiology held in London in 1925, the question of X-ray and radium protection was considered but no definite action was taken. At the second International Congress held in Stockholm in 1928, definite proposals were adopted and subsequently an International Committee on X-Ray and Radium Protection was formed. The recommendations adopted by the International X-Ray and Radium Protection Committee contained no reference, however, to a tolerance dose, merely stating that the known effects to be guarded against were: injuries to the superficial tissues, derangement of the internal organs, and changes in the blood. The report of this committee in 1931 likewise contained no statement of a tolerance dose, but in two subsequent reports (1934 and 1937) the tolerance dose is stated as 0.2 r per day.[4]

It is of interest to search for the basis on which this tolerance dose figure was established. From 1925 to 1932, various individuals published their own opinion on the tolerance dose. A somewhat detailed appraisal of the basis of these opinions is warranted here.

In 1925, Mutscheller[5] published a tolerance dose figure of .01 of an erythema dose* per month, and to quote his publication:

"Several typical good installations and fair averages were taken as a basis for calculating the dose to which the operators are now exposed during the time of one month. Thus it seems that under present conditions and standards accepted at present, it is entirely safe if an operator does not receive every 30 days a dose exceeding .01 of an erythema dose, and from the present status of our knowledge this seems to be the tolerance dose for all conditions of operating roentgen ray tubes for roentgenography, roentgenoscopy, and therapy. This dose, however, is derived from the average of a limited number only of typical examples, and is perhaps not yet sufficiently checked biologically and so it may happen that in the future this dose will have to be changed either to a larger or a smaller practical tolerance dose."

In 1928, Mutscheller[6] again published the same tolerance dose figure, and in 1934 the same figure of .01 of an erythema dose was published for "rays of higher penetration" used for therapeutic

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*An erythema dose is one which produces a perceptible reddening of the skin.

application.[7] The erythema dose for this quality of radiation was given as 340 roentgens. Hence his tolerance dose was then 3.4 r per month 0.1 r per day.

Glocker and Kaupp[8] in 1925, and acting for the German Committee on X-Ray and Radium Protection, published the same figure as .01 of an erythema dose which they took directly from Mutscheller.

Sievert[9] published in 1925 one-tenth of an erythema dose per year as a safe dose, based again upon laboratory and hospital measurements.

Barclay and Cox[10] in 1928 published a figure of .00028 oi an erythema dose as a daily exposure which could be tolerated without effect. They arrived at this figure in the following manner. Two people who had been chronically exposed without known damage were taken as a basis. One was an X-ray technician who had worked for six years and it was judged that the daily exposure which she received was .007 of an erythema dose. The second was a radiologist whose daily exposure was appraised at .0023 of an erythema dose. Barclay and Cox then arbitrarily took 1/25th of the daily exposure to which the X-ray technician was judged to have been exposed over the six-year period, namely .007 of an erythema dose, and arrived at their tolerance figure of .00028 of an erythema dose per day. It should be noted that in both examples exposure was to soft X rays and that the safety factor of 25 was purely arbitrary.

Failla[11] in 1932 published a report on the "tolerance intensity" to which his technicians had been subjected in operating a 4-gram radium installation. This was of the order of .001 of a threshold erythema dose per month (threshold erythema dose taken as 600 roentgens). The measurement of this intensity was done with photographic film by Dr. Edith Quimby. The longest term of employment had been four and a half years. No ill effects from this level of radiation were noted in the technicians. He accordingly adopted .001 of an erythema dose per month (.6 r per month or .02 r per day) as the "tolerance intensity" for gamma rays. In referring to the previously published tolerance dose levels, Failla points out that they were based upon soft X-ray radiation, having a lesser penetration than λ rays and hence less potentiality for damage to internal organs. Since protection from soft X rays is readily obtained, Failla suggests that the figure of .001 of an erythema dose per month be accepted as tolerance for both X rays and λ rays.

Kaye[12] brought together in 1928 the combined opinions on the tolerance dose and converted the figures to .001 of an erythema dose in five days as an average value.

Quality	To produce erythema
Grenz rays	100 r
100 kv	350 r
200 kv	600 r
1000 kv	1000 r
λ rays (radium)	1500 r

The dependence of erythema on quality of radiation is illustrated by the approximate values tabulated. Thus it may be seen that for soft scattered X rays (which were those considered by Mutscheller), the erythema dose may be only 1/5 of that for λ rays of radium which formed the basis of Failla's figure.

The International X-Ray and Radium Commission, acting for the International Congress of Radiology, set the tolerance dose level at 0.2 roentgen per day in both 1934 and 1937 recommendations.[4] As an outgrowth of this International Commission there was formed in the United States an Advisory Committee on X-Ray and Radium Protection which published its first proposals[13] in 1931 in the Bureau of Standards Handbook No. 15. Here the tolerance dose was set at 0.2 roentgen per day. In a later report of this American Advisory Committee (Bureau of Standards Handbook No. 20), the tolerance dose is stated as 0.1 roentgen per day, no explanation being given for this reduction in tolerance dose. In a subsequent publication in 1941 on the subject of Radiation Protection, Taylor,[14] who is Chairman of the American Committee, referred to the safety value of 0.02 roentgen per day. This latter figure, however, is not the combined opinion of the American Advisory Committee but was published independently by Taylor.

Wintz and Rump[15] in a League of Nations Publication of 1931 reviewed the various statements of tolerance dose and came to their own conclusions that the admissible dose is 10^{-5} r/sec assuming an eight-hour working day and 300 working days per year. This amounts to $\sim$.25 r per day. They qualify

this dosage rate for persons remaining in proximity to sources of radiation giving off rays without intermission (radioactive preparations) by reducing it by a factor of 3 (i.e., 0.1 r per day). Both Failla and Wintz and Rump have thus specifically referred to λ rays in defining their tolerance dose. The American recommendations[16] of 0.1 r per day refer to both X and gamma rays.

The difficulties of establishing a tolerance exposure level can be ascertained from the history of its development. A clear-cut experiment on a large scale is virtually impossible to conduct because there would always arise various degrees of abnormality (in blood levels) which would have no relation to radiation exposure. In this respect Taylor concludes:

"Obviously, the determination of this tolerance dose is difficult and at best uncertain. The biologic factor differs too greatly among individuals to permit the use of a sharply defined tolerance. To be well beyond the danger limit, one must apply a generous safety factor to the result of any physical measurements."

THE BIOLOGICAL ASPECTS OF THE TOLERANCE DOSE

Experience thus far has taught that certain fundamental biologic trends will influence the allowable exposure to radiation. This information has been gained through both therapeutic and experimental work with radiation. The problem of tolerance dose is largely concerned with the radiosensitivity of tissues, and for that reason a discussion of radiosensitivity is briefly included here.

Radiosensitivity of Tissues

Radiosensitivity—By radiosensitivity is meant the relative vulnerability to radiation of a tissue living in its normal physiological environment. Although we tend to think of each tissue as having its own inherent radiosensitivity, advances in the application of radiation to medical uses have come about largely by learning to adapt the techniques of exposure to take advantage of the varying sensitivities of different tissues.

Not only may we think of different tissues as having differing radiosensitivities, but different organisms react differently to the same ionizing dose of radiation. There are also variations within strains of the same species. This is one of the obstacles in carrying over to man conclusions based on the biological effects of radiation found in lower animals.

The problem is further complicated by various biological events which can alter the radiosensitivity of a given tissue. A few examples will serve to bring out certain of these factors which are known.

Differentiation—Contrary to the usual principles of pharmacological action, the tissues which are less specialized in function tend to be the more vulnerable to radiation. The degree of specialization of a tissue is referred to as its differentiation. The highly complex cells of the nervous system are apparently less affected by ionizing rays. At the other extreme, the primitive cells of the reproductive or lymphatic system are extremely vulnerable.

Rate of Growth—In general, the more rapidly growing and active cells tend to be the more radiosensitive ones in a given tissue.

Cellular Environment—The composition of the medium or the environment of the cells comprising a tissue strongly affects the radiosensitivity. This is closely associated with the complex physiochemical alterations which must ensue within the cell when it is subjected to unnatural ionization. Whether the effect of the ionization is a direct one, taking place within the cell, or an indirect one resulting from alterations in the environment, is still largely a matter for conjecture, although evidence is accumulating to show that both mechanisms may be active. As an example of the effect of environment upon radiosensitivity, one may cite the diminished effect of radiation upon otherwise extremely radiosensitive tissues when they are subjected to a reduced oxygen supply during the time of exposure. Likewise, there is experimental evidence to show that a change in the acid-base relationship, affecting the permeability

of cell membranes, can, for certain tissues, increase their radiosensitivity. Physical factors such as heat, cold, or previous radiation may alter either the growth rate or environment of the cells, and thus produce a change in their vulnerability to ionization produced in them or in the medium in which they live.

Threshold and Nonthreshold Effects—If one plots a dose-effect graph for various tissues subjected to radiation, there are, in general, two forms which the graph may take:

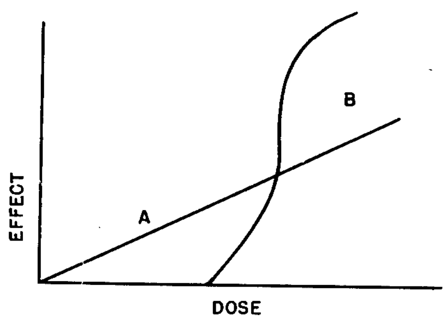

Figure 1.

Curve A illustrates the nonthreshold case, where, as the dose is increased there is a linear increase in the effect. There is no initial threshold of dose which must be exceeded before an effect is obtained. To recognize a nonthreshold effect, it must be readily observable or measurable after exposure to minimal amounts of radiation. An example is the influence of radiation upon the germ plasm of lower organisms.

Curve B illustrates a threshold effect. Here the effect is not measurable by present methods until a certain threshold of dose is exceeded. Threshold effects are not linear with dose but assume some form of S curve. The effects of radiation upon the skin and the blood-forming organs are examples. Until the dose reaches or surpasses the threshold, the first signs of skin effect (erythema) or of effect upon the blood-forming organs (as reflected in the circulating blood) are not seen.

The majority of radiation effects are thought to be of the threshold type. It may be that as more delicate indicators are found to measure effects, more of them will be seen to be of the nonthreshold type.

Reversibility of Effects—The reversibility of radiation effects is important, particularly in occupational exposure. By reversibility is meant the return of a tissue to its previously normal state after exposure is discontinued. The reversibility of any specific effect is dependent upon the reparative or regenerative properties of the tissue. Some tissues, such as skin, the blood-forming elements, membranous linings of the body cavities or glands, and peripheral nerves, are endowed with a special type of repair mechanism. Other tissues, such as brain, kidney, and lens, have no repair mechanism. In them, repair is by the formation of a scar, which does not take over the function of the original tissue which it replaces. The effects in such cases are said to be irreversible.

In order for an effect to be reversible, it must not produce injury beyond the limits of the normal capacity for regeneration. Otherwise the effect is permanent and may lead to complete destruction or exhaustion of the tissue.

Both the total dose and the total time over which it is given may affect the ability of the regenerative processes to function. If the total dose is excessive, irrespective of the time over which it is administered, regeneration and repair may be impossible. On the other hand, a total dose which will produce reversible effects if given at a rate slow enough to permit regeneration may instead result in irreversible damage to the tissues if given over a shorter period.

A tissue which has returned to apparent normal function following radiation damage may not, however, sustain repeated damage and may be unable to regenerate completely. Repeated radiation effect, initially followed by repair, will eventually exhaust the reserve for regeneration and end in death of the tissue. Hence, previously sustained radiation injury (for example to skin) which has apparently been followed by regeneration and return to normal function must be carefully observed and a repetition of

of the injury avoided. Even bone marrow, in spite of its remarkable powers of recovery from radiation injury, will eventually exhaust its recuperative reserve under too frequent or too heavy doses.

General Body Effects

For purposes of simplification, the general body effects will be considered from the standpoint of (1) external radiation and (2) internal radiation. Although the effects are similar in many respects, the source and route of administration of radiation has some bearing on the tolerance dose.

The early toxic signs in man resulting from external radiation are those of (a) general lassitude and fatigue and (b) early demonstrable effects upon the leukocytes of the blood. Radium workers who are subjected to continued overexposure develop a lassitude which is out of all proportion to the physical requirements of their work. This is an effect which is real and should be cause for investigation of possible exposure. From the standpoint of protection, it is fortunate that the leukocytes of the blood furnish so readily available an index of overexposure. An extensive report on the effects of radiation on the blood and blood-forming organs has been given elsewhere (CH^{-410}) so that it will suffice here to briefly describe these early effects.

There is either a diminution in the total number of white blood cells (leukopenia) or the total number of white blood cells may remain within normal limits but there is an altered ratio in the proportion of neutrophils to lymphocytes. This latter alteration in ratio producing a lymphocytosis is more likely to appear with lesser degrees of overexposure. It is not an uncommon finding among radium workers to see an initial instability in the total white blood count for a period of months which later stabilizes on a lower level than was present before exposure began. The red blood cell elements do not participate in the early effects of continued overexposure, but a diminution in the number of red blood cells (anemia) does appear as a late effect of continued overexposure. Fatal anemias which do not respond to any form of treatment have appeared in a considerable number of radiation workers after long continued overexposure. This is a manifestation of bone marrow exhaustion in which repair has not been able to keep up with the continued insult produced by overexposure.

A regular and carefully done blood count on personnel exposed to radiation is thus indicated and serves as an early index of possible overexposure.

By internal radiation is meant radiation received through the ingestion or inhalation of radioactive substances. The earliest experience with internal radiation was obtained through studies of inhaled radon both in animals and in man. The early effects of continued inhalation of radon in excess of the tolerance limits are those upon the blood. Studies of the blood of workers concerned with the separation of radium show an eventual effect upon the blood-producing organs. The magnitude of the exposure can be correlated with the level of radioactivity of the expired air.[17] Similar studies have been made upon the workers concerned with the preparation of mesothorium.[18] The late effects of continued inhalation of excessive amounts of radon are unfortunately known for man. The high incidence of lung cancer in the Schneeberg, Sacony, and Jachymov mines of Bohemia has been directly attributed to breathing air containing radon, which gives an alpha bombardment to the lung tissues. The incidence is high. In one report,[19] out of a total of 89 deaths occurring over a period of 10 years among 400 miners, 60 autopsies were obtained and 42 of the deaths were shown to be due to primary lung cancer. This was an incidence of 9.7 ± 1.5 per year per 1000, or about 30 times the normal expectancy. Of 48 mice kept for a year in the Schneeberg mine, 28 died, 7 having developed tumors of the respiratory organs.[20] The average radon content of the air in these mines is of the order of 3×10^{-12} curie of radon per cc. On the basis of these figures, it is of interest to calculate the internal daily dose to the lungs which resulted in these findings.

We calculate the lung dosage by a combination of the methods of R. D. Evans[21] and Failla.[22] Evans has given a good picture of the lung as a series of tubes of specified length and diameter. From the total absorption of the alpha radiation from radon and its products in the first 35 μ of the tube linings, Evans has assessed the average ionization per cc throughout this lining tissue. Failla in a discussion of beta-ray effects in the lung points out that "lung" cancer in man is essentially carcinoma of the

bronchus. It should therefore be correct to calculate the dose in the bronchus only. This dose is approximately 0.3 rep per day, approximately 20 times that derived as an average throughout the lung. The validity of this method might be checked by the autopsies on the Schneeberg miners, but the site of origin of the carcinoma is not given in the published reports. On the basis of ionization, and allowing for the heavy particle nature of this radiation, 0.01 rep per day would be used as the tolerance dose. This would correspond to a tolerance concentration of 10^{-13} curie per cc. This, in fact, is the concentration widely accepted in Europe and used in several states. The permissible tolerance concentration of radon recommended by the American Bureau of Standards is 10^{-14} curie per cc of air. In view of the uncertainties of the lung calculations, this additional safety factor seems to be well chosen.

The radioactive gases which in the past have been an occupational hazard were the emanations from radium and mesothorium. Our present activities bring us in contact with other new radioactive gases (xenon, argon, krypton) and a radioactive vapor (iodine). In the case of xenon, it is necessary to consider the hazard both from the standpoint of internal radiation (inhalation) and external whole body radiation from the beta and gamma rays of xenon in the atmosphere. Calculations indicate that the external radiation from radioactive xenon determines the permissible concentration in the atmosphere, which has, for the purpose of plant design, been set at 2×10^{-14} curie/cc.

The tolerance value for radioactive iodine in the atmosphere is based upon the selective absorption and deposition of iodine in the thyroid gland. Calculations on the permissible atmospheric concentration of radioactive iodine, for exposure over 24 hours a day, has been tentatively placed at 1.0×10^{-13} curie per cc.

Internal radiation from ingestion and deposit of radioactive material in the body was first encountered by Martland[23] among the radium dial painters. The history of this occupational disease is well known. About 98 to 99 per cent of the radium which was ingested through the habit of pointing the brushes in the mouth was excreted, but the remainder was deposited in the body, largely in the bones. As little as 1 to 2 micrograms has proven to be a lethal dose. Here again the continued bombardment of bone marrow results either in a fatal anemia or in the production of malignant bone tumors. The late signs of damage, anemia, or malignant bone tumors, may be evident some years after exposure has resulted in the deposit of radium. Martland does not record the early signs of radium deposit, as he had no opportunity to do so. It is possible, however, to detect radioactivity in the expired air as an early check on overexposure, and this is done routinely by the more cautious plants producing luminous dials. The alteration in blood count as an early sign of overexposure to radon was noted before. The same finding could in all probability be detected as an early sign in radium poisoning if it were looked for. There is apparently a compensatory activity of the bone marrow which attempts to keep pace with the tissue destruction produced by the continued alpha bombardment but eventually leads to bone marrow exhaustion and fatal anemia. Experience with radium poisoning in the luminous dial industry has led the Bureau of Standards to establish 0.1 microgram of radium as the limit which can be deposited in the body without resulting in later damage.[24]

The hazards of internal radiation from ingestion or inhalation and eventual deposit of radioactive materials in the body cannot be overlooked in the present undertaking. The fission products are the source of this radioactive material. Studies on the absorption, deposition, and excretion of the various fission products are being made and reports have appeared by Dr. Hamilton and his associates. Tolerance values for the limits of the fission products which could be safely taken into the body cannot be set until a complete study has been made of all the fission products and their effects are known. With the exception of the gaseous fission products (xenon and iodine), protective measures must proceed on the basis of completely eliminating this hazard.

Skin Effects

The effects of radiation on the human skin gave the first indication of any biologic effect of X rays and gamma rays. Becquerel, who carried a tube of radium in his vest pocket for demonstration purposes,

developed a reaction of the underlying skin. X-ray dermatitis was in evidence within a few months after the discovery of X rays.

The greatest number of radiation injuries have been those to the skin both in X-ray and radium workers. Following the early wave of damage to the skin which came in the first 15 years of X-ray and radium experience, there were more precautions taken to prevent skin damage. With special attention given to local protection, the number of injuries to the blood-forming organs increased due to lack of complete protection. An emphasis was then placed on whole body protection; the skin injuries again assumed first place and at the present time they are still appearing in unnecessary numbers. The majority of these are physicians or dentists; a fewer number appear in radium workers.

The characteristic effect of large doses of X ray and radium upon the skin is the production of a skin erythema. In this respect, they are comparable to ultraviolet radiation except that the latent period between exposure and erythema is delayed up to $\sim$4 weeks with single X ray and radium exposure depending on the dose. As was previously noted, there is a variation on the dose-effect ratio to produce erythema with rays of varying quality, in the direction of a larger dose for shorter wavelength. As the length of time over which the radiation is administered is increased, the dose required to produce erythema becomes larger.

The erythema is the result of a dilation of the fine capillaries, venules, and arterioles supplying the skin. The mechanism is thought to be identical with the erythema produced by ultraviolet irradiation[25] having a wavelength of $\sim$ 300 $\mu\mu$, which is the effective component of sunlight. The stimulus which produces the blood vessel dilation is thought to be due to a release of a "histamine-like" substance from the living superficial layers of the skin.

The skin is composed of essentially two layers of tissue—the epidermis which consists of the epithelial cells forming the protective covering of the body and the dermis lying beneath the epidermis, which consists of the supporting connective tissue for the epidermis, and carries the nutrient vessels, accessory organs, and nerve supply. The thickness of the epidermis, or outer cellular layer, varies over the body but, in general, ranges from 0.07 to 0.12 mm. On the palmar surface of hands and fingers, it averages $\sim$0.8 mm, on the soles of feet $\sim$1.4 mm. In men accustomed to heavy labor which produces a compensatory thickening of the skin of the hands, the epidermis may be considerably thicker. The outermost layer of the epidermis (stratum corneum) consists of dead, hornified, flattened cells. The thickness of this outer horny layer varies over the body, being thickest on the soles ($\sim$.8 mm) and palms ($\sim$.44 mm). On the backs of the hands and over the remainder of the body it is considerably thinner, <u>but even a thickness of 0.1 mm would give protection against natural alpha and very low energy beta radiation.</u> As cells are lost from this outer layer by normal wear and tear, the underlying growing layer of the epidermis continues to furnish a new supply. There are no blood vessels within the epidermis—the fine capillaries nearest the surface lying directly beneath the epidermis. Thus, erythema is produced <u>below</u> the epidermis. Damage to the skin (whether thermal, irradiation, or chemical) is produced in the living and growing layers of the epidermis (which are shed or desquamated following the injury), or if more severe, damage may also appear in the deeper tissues resulting in necrosis, ulceration, and thrombosis (closure of the vessels).

The thickness of the outer horny layer of the skin is of importance in relation to the penetrability of alpha and low energy beta radiation. Since the alpha particles of uranium have a range in tissue of $\sim$.05 mm, one would not expect skin injury from them. When the energy of alpha particles is greater (as those from a cyclotron), penetration in tissue becomes sufficiently great to produce skin injury.[26]

The beta-ray penetration of tissue is discussed at some length in a report by one of us (CH-930). It is sufficient here to emphasize that beta particles of the average energy associated with long-lived fission products will penetrate well below the skin, and hence there is real potentiality for injury if due caution is not exercised to avoid overexposure.

The previous discussion of erythema applies to radiation injury of a relatively acute type. The dose required to produce erythema is relatively high. As the time over which the dose is administered

is lengthened to one or more years (as in occupational exposure), a considerably higher total exposure can be tolerated. Erythema may be an early sign when the dose has been acute, but it may not appear at all when the exposure is spread over a period of years. Hence, one cannot rely upon the appearance of an erythema to judge whether or not overexposure is producing damage when the exposure is prolonged over years. Other signs which should prove a warning are a loss of the normal skin ridges of the finger tips, loss of hair on the back of fingers and hand, cracking, brittleness, or ridging of the fingernails, a loss of the normal sensitivity, and an abnormal dryness of the skin.

The late evidence of injury appears as telangiectasis (a permanent capillary dilation), pigmentation, atrophy of the skin and its appendages (hair follicles, sweat, and subaceous glands), and skin thickening with the appearance of wart-like growths. The most serious late sign of damage is ulceration, which usually results from minor abrasions which fail to heal. The ulceration in many cases eventually progresses to cancer of the skin which in some 25 per cent[27] spreads beyond the hands and proves lethal. The time between onset of exposure to the recognition of skin cancer in one series was an average of nine years. The age of these victims ranged from 28 to 60 years, whereas cancer of the skin appearing without relation to radiation is an uncommon disease in early and middle life.

Stone and Larkin[28] have found that 110 n will produce a threshold pigmentation of the skin from the 4th to the 19th day, which is an effect produced by 650 to 700 r of 200 kv X rays. Thus, for fast neutron exposure there is a ratio of effect varying by a factor of 6 for the skin, which is accounted for in the tolerance dose level for fast neutron exposure of 0.01 n (0.025 rep) per day.

Unfortunately, the workers who have been damaged have no record of the exposures received over a period of years. There is no general agreement on skin tolerance among radiologists or physicists who have medical experience. On inquiry from two professors of radiology of wide experience, the answers varied from 0.5 to 5.0 r per day of X ray to the hands. In contrast to our statement under General Body Effects, many radiologists and physicists would be willing to accept 1 r per day to the hands occasionally if special work make it necessary. Past experience with fluoroscopy and radium handling leads us to assume, however, that for long-continued exposure over a period of years, a limit of 0.1 r per day exposure of the skin to radiation which will effectively penetrate below the outer horny layer (0.1 mm) is a safe limit.

Effects on Reproductive Organs

The reproductive organs may sustain damage either to the germ plasm or to the cells which carry the germ plasm (ova or sperm). The most sensitive elements in the reproductive organs are the parent cells which eventually give rise to the mature ova or sperm. Other cellular elements in the reproductive organs which are concerned with internal secretion and control the desire for and ability to consumate the sexual act are relatively radioresistant. To obtain a permanent sterilization of the female ovary requires some 400 to 600 r delivered within the ovary. Sterilization in man is produced by 800 to 1000 r in the testes. There is a threshold of dose which must be exceeded before any effect upon fertility becomes manifest.

Experiments in progress by Heston and Lorenz[29] have already shown that continued exposure of female mice to 1 r per 8 hours daily produces ovarian folliclar atrophy after approximately 540 r. Experiments by Russ and Scott[30] show that continued exposure to gamma radiation 20 times in excess of tolerance leads to a reduction in fertility in mice.

The possibility of damage to the reproductive organs is the most discussed and feared hazard in the minds of most nonmedical personnel who work with radiation. The incidence of reduced fertility following occupational exposure is not accurately known, but it is not great in comparison with damage to skin. The reasons for the keen interest in the subject can best be learned from Freud. But one cannot dismiss these fears lightly as animal experimentation indicates that at least in animals, the safety factor in 0.1 r per day may not be as great as 10. Whether one can transpose these results to the human is not known—are assuming here that they are applicable.

Radiogenetic Effects

In 1927 Muller[31] demonstrated that the mutation* rate of the fruit fly could be accelerated by exposure to X rays. Bagg and Little[32] and Snell[33] have produced radiation-induced mutations in mice. Radiation increases the rate of appearance of common mutations which occur spontaneously; it produces the uncommon ones only rarely. Single exposures of 30 to 40 r will double the mutation rate in the fruit fly; doses of 500 r are required to produce mutations in mice, and these appear in far lower incidence than in the fruit fly.

Radiation-induced mutations have been found to have characteristics which bear on the practical consideration of radiogenetic changes possibly associated with occupational exposure. The most important of these is that there is a linear relationship between dose and increase in mutation rate. There is no threshold effect—the cumulation of exposure is thus additive. Further more, the magnitude of the effect is independent of the wavelength and dosage rate of exposure.[34] These genetic studies (largely in the fruit fly) have lead to considerable discussion concerning their applicability to man in relation to tolerance dose. There are workers in the field who advocate a further reduction in the tolerance dose for X and gamma rays because of the nonthreshold effect of X rays upon the germ plasm of the fruit fly. Further concern is added to these fears by the possibility of even greater radiogenetic damage from heavy particle radiation (neutrons, protons, etc.) than from the more familiar X and gamma rays.

Mutations, whether spontaneous or produced by radiation, are about 90 per cent lethal or sublethal. This means that the offspring does not survive the gestation or hatching period, or dies shortly thereafter. The lethal mutations are either dominant or recessive. By dominant is meant that, for the exposed parent organism, the lethal effect appears in some of its direct offspring. By recessive is meant that the effect might appear only in some succeeding generation of the radiated subject. In man it would appear in the near descendants only should cousins or near relatives intermarry. It has been calculated from the laws of genetics that some 5000 years would be required for a mutated gene to meet another mutated gene descended from the original mutation. This would indicate that we need not be too concerned about the recessive deleterious effects of mutations.

The viable mutations (about 5 per cent of all mutations, whether spontaneous or produced by radiation) are about 95 per cent deleterious ones. Of these, the majority (about 96 per cent) pertain to other than the sex chromosomes. The remaining are sex-linked mutations,† appearing in the sons of the daughters of the sperm carrying the mutated gene. The spontaneous rate of appearance of these dominant deleterious yet viable mutations (which constitute about 4 per cent of all mutations) is about 1:2700. It has been calculated that an accumulated dose of 300 r in the female will raise this probability to 1:230.[34]

Our present knowledge of radiogenetics has been gained entirely from experimental studies in the fruit fly or other lower organisms, and to a lesser extent in mice. Actually, very little is known about genetics in man, and still less about the effects which might be produced by exposure to radiation. As yet there is no convincing evidence to indicate that the present generations of radiation workers have produced offsprings which differ from those of the general population. It can be argued, however, that succeeding generations or intermarrying may bring abnormalities to light. If experimental finding in the lower organisms are accepted as valid for man, then one can only escape some degree of radiogenetic effect by avoidance of all radiation exposure, including the natural radiation (cosmic, etc.).

This concept has lead Henshaw[3] to suggest that perhaps for the nonthreshold reactions one should define rather a "tolerance injury" than a "tolerance dose."

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* A mutation is an hereditarily transmissible abrupt alteration in germ plasm.

† Based on the number of chromosomes in the female (48) and male (47) the chance is further reduced by a factor of 1: 24 in the female and 1: 47 in the male.

For those readers who wish to pursue the subject further, we would refer you to Henshaw's paper.[3]

THE DEPENDENCE OF TOLERANCE DOSE ON THE NATURE OF THE RADIATION

Specific Ionization

Experimental as well as clinical studies have shown that the biologic effect produced by the absorption of a given quantity of energy is dependent in part upon the nature of the incident radiation. The effects are produced in some manner by the ionization resulting from the impinging radiation, but the distribution of ionization is not the same for all qualities of radiation. A greater ion density along the path of an ionizing particle is associated with a more pronounced cellular or biological effect. The density of ionization per unit length of path is referred to as the specific ionization of a particular quality or type of radiation. One can then compare biological effects produced by equivalent energy absorption from X rays, gamma rays, neutrons, etc. A detailed and critical analysis of this phenomenon is reviewed by Zirkle.[35] We refer to it here because it is convenient to consider tolerance dose from the point of view of the type of radiation involved rather than in terms of the specific effect on the various parts of the body as in the foregoing section. The evidence comes from the same sources and some repetition is inevitable.

X-Rays

As our knowledge of permissible exposure has been derived almost exclusively from experience in hospitals, it is best founded for X radiation. In particular, the original choice of tolerance dose was founded on two cases, both involving the exposure of operators to scattered radiation only. The wavelength of this radiation can be taken as 0.3A. Hence its penetration in tissue is about 96 per cent at 1 cm deep and 25 per cent at 10 cm deep. (These figures are derived from a consideration of the scattering contribution in a body subjected to wide beam irradiation. The corresponding figures from the absorption coefficient alone would be 80 per cent and 8 per cent, respectively.)

The tolerance dose supposedly has a safety factor of the order of 20 to 40 for radiation of this type. Modern practice involves shielding the operator by lead screens, but it is permitted that directly transmitted radiation falls on the operator, up to the limiting tolerance amount. Under these conditions, the net effect on the deeper seated organs may be different. This is especially the case with the modern high voltage machines. Four hundred kv radiation is as common now as 150 kv was when tolerance was first established. Penetration of this radiation is about 100 per cent at 1 cm and 50 per cent at 10 cm (ninety per cent and 30 per cent, respectively, from the absorption coefficient) and we might consider its effect on the hemopoietic system as approximately twice as damaging.

Little has been written about the damaging effects of X radiation generated in the range between 400 kv and 1200 kv. Such hospital installations have, in general, been well protected and have not been operated many hours per day except in recent years. In this range of voltage there is little increase in the "percentage depth dose" for depths up to about 10 cm, for wide beam irradiation. The increased penetration of the primary beam is offset by the reduced contribution from scattering. It is also known that the effect of these radiations in therapeutic dosage is quite closely the same in deep tissue as that of the well studied 200 kv radiations. As far as skin effects are concerned, there are two familiar effects both of which indicate that for equal dose as usually measured, the damage by high voltage radiation should be less severe. It is reasonable to suppose that a tolerance dose established for 200 kv radiation with a margin of safety of 10 or more will still be safe for X radiation up to 1200 kv. The widespread industrial use of 1000 kv radiation in the present war would give a fruitful source of study in a few years if the exposures were adequately recorded. Unfortunately, although it is known that many operators are being exposed to radiation in excess of 0.1 r per day, good records are the exception.

Gamma Rays

Adequate experience with gamma radiation has been restricted to that from radium and its products, and again it is derived from handling in hospitals. It has long been accepted that the danger of exposure to gamma radiation exceeds that from X radiation for two reasons: (1) X rays can be "turned off" when not required, (2) the gamma-ray penetration is higher. Wintz and Rump,[15] who gave the first consideration to gamma-ray exposure, select a dosage rate of $1/3 \times 10^{-5}$ r/sec as against 10^{-5} r/sec for X radiation. The latter figure is based on an eight hour day and the former apparently implies possible exposure to gamma radiation for 24 hours per day. In the alternative expression of tolerance dose as a daily amount, Wintz and Rump would make no distinction. On the basis of penetration (94 per cent at 1 cm, 58 per cent at 10 cm without backscatter), one might have a factor of 2 or 3 to represent the additional total body ionization.

It is commonly supposed that the effect of gamma radiation on the body is greater than that for X rays for equal surface dose solely on account of the greater penetration. (It is assumed that the action of the radiation is entirely due to the secondary electrons liberated and that change of specific ionization over this range is not important). Hence the method of expressing tolerance dose in terms of the total ionization has recently gained favor, especially abroad. The unit employed for this purpose is the "gramme-roentgen." The body exposure on this basis is simply the integral $\int D(s)\, dV$, where $D(s)$ is the dose in roentgens as a function of position s in the body, and we take the density of tissue as 1. Now $D(s) = Kn(s)$ where $n(s)$ is the number of ion pairs per cc of tissue. The integral is kN where N is the total number of ion pairs produced. One gramme-roentgen corresponds to 1.6×10^{12} ion pairs.*

Simple computations will show that there is more change in total ionization as a result of geometry than results from the change from soft X rays to gamma rays. For equal surface dose we have

	Relative total-body ionization
Soft X rays from large distance	~ 1
γ rays from large distance	2.5
γ rays from point source at 100 cm	1.9
γ rays from point source at 10 cm	0.6

The gramme-roentgen point of view may have more significance under conditions in which only a part of the body is exposed to radiation. At the present time there is insufficient experience to apply the method in general. It is tacitly involved in the standard protective devices for assembling radium sources wherein the hands, forearms, and head are irradiated rather liberally. Emphasis on the gramme-roentgen implies that the principal cause of damage is the general body effect. Among the present group of radium workers, the principal observed effect is skin damage, particularly to the hands. This is believed due to greater exposure of the hands, rather than to greater sensitivity, but it does indicate that the permissible exposure is not safe by much more than one order of magnitude and hence that little is to be gained by elaborating the gramme-roentgen aspect.

Exposure to gamma radiation from internal sources can be treated in terms of the ionization produced in tissue. In general, the effect would be exceeded by that of the accompanying beta radiation.

Beta Rays

There is no sound evidence on the permissible exposure of the body to beta radiation. The handling of strong sources was not common until the development of artificial radioactivity, especially by the

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*Dose in roentgens is frequently thought of as "dose per cc," which could lead to "total dose" in the above integration. This fundamental error should be eradicated. Dose in roentgens is a measure of the ionization per cc, and is independent of the size of field or volume of tissue irradiated (increased scattering, etc. is included in the measurement of 'r').

cyclotron. (This is not strictly correct inasmuch as cathode ray tubes, e.g. Lenard tubes, have been widely used, and these are potent enough sources. With such an installation it is relatively easy to maintain adequate shielding at all times. Consequently there seems to be no record of damage by prolonged exposure to these radiations. The numerous cases of exposure, accidental or otherwise, to stray beams for short intervals is not discussed here.)

It is generally conceded that the effect of X rays and gamma rays on tissue arises from the electrons generated in tissue by these radiations. Hence, for equal ionization, beta radiation should produce the same effect,* apart from a possible correction due to specific ionization differences. This has been sufficiently well confirmed by experiments at therapeutic levels. One can therefore confidently state that an exposure to beta radiation of 0.1 rep/day will be safe. Since the external beta-ray effect is confined to the skin or to tissue within perhaps 1 cm of the skin, it is evident that beta radiation will add little or no contribution to the general body effect. On this basis, many radiotherapists would permit exposures up to 1 rep day. In view of the high percentage of superficial damage among the present workers,† one doubts whether this is entirely justified. Nevertheless, if the full spectrum of beta radiation is allowed to contribute to the ionization, the limit 0.1 rep/day imposes rather tight restrictions on the handling of beta-active materials. It can be supposed that beta rays that fail to penetrate the hornified layer will be clinically insignificant. The thickness of this layer will be taken as 0.1 mm. Thus the provisional tolerance dose for external beta radiation will be 0.1 rep/day measured in a chamber of wall thickness 10 mg/cm^2. Damage arising from the ingestion or inhalation of active material has be assessed in terms of the ionization with zero absorber.

Neutrons

The effects of prolonged exposure to low intensity beams of neutrons is unknown. Many effects of higher intensity neutron irradiation of biological materials have been compared with X-ray or gamma-ray irradiation. In this work, the neutron dose has frequently been quoted in "n" units as the reading of a particular Victoreen condenser chamber. The ionizing effect of fast neutrons in the body can be considered equivalent to 2.5 r/"n." The biological effectiveness of neutrons relative to X rays varies widely for different materials or for different conditions in the same material. According to Zirkle,[31] the effects on mammalian tissues show effectiveness ratios ranging from 5 to 9 (in terms of r to "n"), although there is a distinct possibility that injurious effects on mammals exist with effectiveness ratios as high as 25.

From these figures, it has become common practice to consider 0.01 n (0.025 rep) as a tolerance dose of comparable safety to 0.1 r for X rays. The most conservative would quote 0.004 n, corresponding to 0.01 rep. The figure of 0.01 n (0.025 rep) per day appears to be adequately safe, if the supposed safety factor for the X-ray dose is as high as 20.

Whereas the possible effects of prolonged fast neutron exposures have to be deduced, with some show of logic, from the known therapeutic ratios, the effects of exposure to slow neutrons is at present entirely unknown. Presumably three factors should be taken into account:

1) The production of gamma rays in the body.

2) The production of protons by the neutron reaction on some of the constituent atoms.

3) The production of new atomic nuclei.

Of these three, the first can be taken care of by ionization measurements. Whether (2) or (3) will have biological significance at the exposure levels limited by (1) remains to be investigated. In general, the body would not be subjected to slow neutron irradiation without the admixture of gamma radiation or fast neutrons. One might anticipate that the permissible exposure would be limited by the total gamma radiation or the fast neutron effect, before (2) and (3) became important.

* For a more detailed consideration on some of the physical aspects of the effects of beta radiation on tissue, the reader is referred to CH-930, H. M. Parker.

† Workers in industry using X ray, radium, etc.

Alpha Rays

For external radiation, the penetration of natural alpha particles is well below the thickness of the "absorbing layer." The damaging effect is assumed zero unless the intensity is such as to physically burn the part. There is now some clinical evidence to substantiate this point as uranium sheet has been worn in contact with the skin for several months. The observed damage was nil for this exposure corresponding to $\sim$ 250 rep/day, although possible late damage has to be considered.

Internally, the effects are computed in terms of the ionization produced. Since the increased biological effectiveness of neutron-produced ionization is believed due mainly to the high specific ionization along the proton tracks, it is to be expected that alpha particles would be even more effective. A tolerance dose of 0.01 rep/day would be reasonable.

Since the effects are limited to the ingestion or inhalation of alpha-ray emitters, they have been adequately treated as the special problems of bone and lung damage.

Protons and Other Particles

Accelerated particles can produce damage to the skin and superficial structures. Such exposures occur as occasional accidents. It is not appropriate to discuss these hazards in terms of tolerance dose. If it became necessary to establish a tolerance dose for protons, the figure of .025 rep/day would be proposed by analogy with the fast neutron exposure, which is essentially a proton action.

Combined Radiations

The body will, in general, be exposed to more than one type of radiation either simultaneously or at various times during a career associated with radiation work. In the absence of contrary evidence, it will be supposed that the summated daily tissue ionization, properly weighed for the specific ionization factors that have led to different tolerance doses for the heavy particle cases, should not exceed the equivalent of 0.1 rem/day. In general, one would have

$$\left[I_x + I_\gamma + I_\beta + 10\, I_n + 10\, I_\alpha\ 4\, I_p\right] \leqq 0.1 \text{ rem/day} \qquad (1)$$

where the terms represent the ionization contributions of the various radiations as measured, say, in a Bakelite chamber. In a "tissue" chamber, I_n would have a weight factor of only 4, and all the terms would have the significance of "energy absorption" measurements. Slow neutron effects would contribute to I_γ and I_p in this case.

As a working policy, this formula is of the little use at the present time because the composition of the mixed beam will be unknown. If n, γ, or p terms occur, the summated ionization will have to be kept low on account of the large weighing factors. For example, with I_γ and I_n terms alone let I_γ = .09 r and I_n = .001 n. Then $I_\gamma + I_n$ = .09 + 10 x .001 = 0.1 rem. But if the beam composition is unknown, one must ascribe all the radiation to the more dangerous component. Thus,

$$I_r + I_n = 0 + 10 \times .091 = .91 \text{ rem}$$

Or the protective measures are made too stringent by a factor of over 9. Even if one could assume that the observed ionization was divided equally between the gamma and n effects one has

$$I_\gamma'' + I_n'' = .0455 + 10 \times .0455 = \sim .5 \text{ rem}$$

So that the damaging effect is still exaggerated by a factor of 3. The value of analyzing the radiation into its components is apparent, especially the determination of the upper limit of n, α, and p terms.

Some Geometrical Considerations

The estimation of the dose received by the body is normally founded on the reading at one region, e.g., the chest. Conditions can arise under which such a reading may be unreliable. The principal causes are:

1) directional radiation

2) limited or subdivided beams

Under (1), it is clear that anterior and posterior chambers on the body could give readings differing by a factor of 10. If, for example, the beam always entered the back and was always read by an anterior chamber, a serious error would be made. Such conditions can arise where an operator maintains a fixed position at a control desk and is inadvertently irradiated from an unfavorable direction.

Under (2) one has such well-known effects as the overexposure of hands and head while assembling radium source behind a lead screen. The recording chamber would, in general, be shielded by a factor of, say, 10, for equal distance. Then, since the hands might easily be much closer to the source, the net effect could be $\sim$ 150 times greater than that recorded. If the source were mixed beta and gamma, an additional factor between 10 and 50 would come in. Another aspect of limited beams arises in the shielding of equipment which requires controls to be brought to the outside, and in the use of boxes and vats with removable lids or plugs. Good design of such boxes calls for the elimination of strong narrow beams. Great attention has been paid to the blocking of fine beams in X-ray installations. This is relatively easy where the protective thicknesses involved are of the order of a few millimeters of lead. The same precautions are necessary in a large-scale project. A large shield perforated by fine holes in a regular pattern is a case in point. One is compelled to limit the permissible exposure to that corresponding to the high dosage rate in each subdivided beam, for two reasons:

a) Although it is known that a considerably higher dose can be given to a small field than to a large one, the difference is not great enough to justify a change in tolerance dose. Moreover, the clinical picture is complicated if there is a regular pattern of small fields.

b) If the exposure is measured on the person, there is the risk that the measuring device will be continuously carried in an unexposed region. For example, a man could walk by a long shield with holes on an 8-inch square lattice without exposing a film or chamber. A trivial solution of this case is the provision of a suitably sloping floor, but, in general, the possibility of patterned exposure must be excluded. These problems are concerned as much with protection as with tolerance dose and cannot be elaborated here. It is sufficient to indicate that the use of any piece of equipment capable of giving narrow emergent beams invalidates the record of pocket meters in the vicinity.

Measurement of Dose

The limitation of permissible exposure to .1 rem equivalent per day in the sense of equation 1 is futile unless steps be taken to insure that the personnel receives no more than this amount routinely. This can be done in two ways:

1) All fixed radiating sources must be shielded so that the radiation escaping is well below the tolerance level.

2) The exposure of a person in a potentially dangerous area must be recorded by a suitable device on the person.

THE LEGAL STATUS OF THE TOLERANCE DOSE

The legal status of radiation safety recommendations is discussed by Lauriston Taylor.[36] He states that the "legal status of roentgen ray safety recommendations was brought up at the outset and it is important to note that in no country do such recommendations have strictly legal recognition." The complications of this were early recognized and the British Committee, for example, felt that public

opinion could be just as effective as word of law. Moreover, by not having a legal status, the recommendations could remain flexible and be readily changed to suit changing conditions. Laws, once formed, change slowly, and in the matter of roentgen ray protection, such inflexibility may lead to complications.

"The method found by the British Committee to be most effective in bringing about acceptance of the recommendation, was to put the power of inspection and approval in the hands of the National Physical Laboratory*. . . . ."

"In this country, the same conditions* did not exist, and, while recommendations have been accepted,† there is neither legal status nor the authorization for a central laboratory to put weight behind an enforcement. The charter of the National Bureau of Standards does not foster any general outside inspection of activities, nor have funds ever been authorized for the purpose. This bureau does, however, test and certify protective materials and concurs in the recommendations of the Safety Committee."

The National Bureau of Standards Handbook No. 20 on X-ray Protection[16] explicitly states in the first paragraph. "Throughout these recommendations the word 'shall' is used to indicate necessary requirements, while the word 'should' indicates advisory requirements to be applied when possible." This is included under "General Recommendations" and this is in line with Taylor's statement that the Bureau of Standards does concur in the recommendations of the Safety Committee.

Again in 1932, in discussing the work of the American Advisory Committee on X-ray and Radium Protection, Taylor[37] states that "the question of the legal status of these recommendations has been frequently raised. They have none. The Committee feels that none is needed; that legislative enactment tends to stunt development and prevent health changes. We are free to admit that our present proposals may require changes in the future as thay are developed. We wish nothing to interfere with the freedom for modification. It should be pointed out, however, that lack of legal standing will probably not in any way detract from their legal value. They are a recognized set of recommendations, drawn up by qualified representatives of the art and freely distributed to those interested. A court decision involving X-ray protection would, in all probability, for lack of another source, be guided by these recommendations, and persons ignoring them may be held liable for negligence."

Certain states have set up, through their Departments of Labor and Industry, rules to cover the safety of workers engaged in luminous dial painting. New York has compromised on an allowable concentration of 10^{-10} curie of radon per liter in the working air. Massachusetts has prescribed that the whole body exposure to gamma rays shall be maintained at less than 0.1 r per eight-hour day. But insofar as we can determine, in no state are these departmental rulings or recommendations actually law on the statute books. It would seem that the time is appropriate for some government agency to establish and enforce adequate radiation protection in industry. This might well be under the direction of the United States Public Health Service, or through this agency collaborating with State Departments of Public Health. The enormous increase in the use of industrial radiography and luminous dial painting brought on by the war will continue in postwar years on a reduced but still larger scale than preceding the war.

Whether similar agencies can or should undertake to regulate radiation exposure relative to medical uses is a more complicated decision and undertaking. The continuance of damage to medical X-ray and radium workers is evidence, however, that either the medical and dental profession must put its own house in order, or accept direction in this respect from a public health agency.

In considering the radiation damage which continues, both in industrial and medical usage of radiation, we are not entirely in agreement with Lauriston Taylor that "legislative enactment tends to stunt development and prevent healthy changes." The same argument has not prevented legislation protecting the public from overexposure to lead, benzol, carbon monoxide, and a host of other toxins.

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* A national laboratory with powers of inspection and approval.

† The recommendations of the American Advisory Committee have been accepted and published by the Bureau of Standards.

THE APPLICABILITY OF ANIMAL EXPERIMENTATION TO TOLERANCE DOSE IN MAN

In reviewing the subject of tolerance dose, it is most striking that animal experimental evidence has played practically no part in arriving at present day levels. In summary, there are only three tolerance levels which have been established and accepted as a working basis for occupational exposure:

0.1 r per day for external X and gamma radiation

1 x 10^{-14} curie/cc for radon in the air of working rooms

0.1 microgram of radium as the maximum allowable amount deposited in the body of a radium dial painter

Each of these levels has been established by adding a safety factor to the amount which has been known to produce lasting injury to persons so exposed. It is of interest also to note that in each case the safety factor does not exceed 10, and is more likely considerably less than 10. Human misfortune rather than animal experimentation was the basis for these levels.

The past literature is surprisingly lacking in animal exposure carried on with radiation at tolerance or near tolerance levels. This can be explained by several factors:

1) Radiologists have not given much attention to the subject as a whole. One cannot then expect to find considerable experimental work in a field which was relegated to a few committees of the various societies.

2) Experiments within tolerance or near tolerance range require long periods of time and large numbers of animals to complete. They are therefore expensive and time consuming.

3) There may have been the feeling by those engaged in radiobiology that other fields offered more fruitful paths since "tolerance" for mice, rabbits, guinea pigs, or fruit flies still was not "tolerance" for man and could never be proven to be so.

With the awakened interest in tolerance dose, one may well consider how one can apply the knowledge gained from animal experimentation to either a revision or confirmation of existing levels.

In judging that a certain level of radiation cannot be tolerated, one must look for the earliest signs of an injury which is lasting and damaging to the economy of the organism. This implies that we can establish normal standards within fairly well-defined limits and can also control other toxic agents which might either directly or indirectly produce effects confused with those resulting from radiation. These restrictions also interfere with observations on large groups of men under observation for overexposure to radiation, and at the same time are not so easily controlled. Within limits, then, we might conclude that animal experimentation could approach the problem from the standpoint of radiation effect with more chance of controlling the extraneous factors which produce alterations in leukocytic levels, weight, fertility, longevity, or whatever effects we may wish to follow.

Animal research also has the advantage of being able to sample the body elements and functions more completely by selective autopsy. It can also follow the animal to his death, either natural or radiation-induced. It is rare in clinical research to be able to observe any large group over a period of years.

The most important advantage of animal research, however, lies in the possibility of exposing the animals to known quantities and qualities of radiation and at exposure rates which are known.

What then can we expect by way of clarification of human tolerance levels from these advantages offered by experimental radiobiology?

We have already been given some insight into the variation in expected biological effect when the organism is submitted to various qualities of radiation. Some observations had previously been made from radiotherapy. More precise studies such as those now in progress by Zirkle will be of value in formulating tolerance levels for neutrons.

Animal experimentation could also be expected to give information on the relative importance of exposure rate within tolerance or near tolerance limits.

Breeding experiments with animals living in tolerance atmospheres and carried on for generations with sufficient controls would be of value in evaluating the perplexing problem of radiogenetics.

Histopathologic and metabolic studies can indicate important damage unsuspected from gross or clinical examination and perhaps eventually lead to the development of more sensitive indices than are now available to judge overexposure to radiation.

These in the main are the contributions to the subject of human tolerance dose which we might hope to gain from animal research.

The important question arises, however, as to how far we can trust animal experiments when the information must be carried over to man and his protection. Several instances in which this transposition has broken down have already come to light. Evans has found that rats will tolerate quantities of deposited radium which would be lethal to a man. Studies on the tolerance of skin in animals cannot be applicable to man because of the very great difference between the skin of man and the various laboratory animals. Nor is it expected that a group of men could submit to a daily exposure of 8 r per day of gamma radiation up to a total dose of 1350 r without serious impairment of hemopoietic function as evidence in the circulating blood, as has been done with a group of inbred mice.[29]

These observations, though at variance with animal research, do not invalidate all results obtained in animals. They indicate rather that we must look to animal research for as precise information as it can give on qualitative and quantitive effects in the animals. From there on it is a matter for experience and judgment to use the information in evaluating human reactions. The more precise the animal research is made, the more valuable will the information be to those interested in radiation protection.

REFERENCES

1. Rollins, W., Vacuum tube burns, Boston Med. and Surg. 146:39 (1902).
2. Russ, S., Hard and soft X rays, Arch. Roentgen Ray, London, 19:323–325 (1914–1915).
3. Henshaw, Paul S, Biologic significance of the tolerance dose in X-ray, and Radium Protection, J. Nat. Cancer Institute 1:789–805 (1941).
4. International recommendations for X-ray and radium protection, Radiology 23:682–685 (1934); Radiology 30:511–515 (1937).
5. Mutscheller, A., Physical standards of protection against roentgen ray dangers, Am. J. Roentgenol. 13:65 (1925).
6. Mutscheller, A., Safety standards of protection against X-ray dangers, Radiology 10:468 (1928).
7. Mutscheller, A., More on X-ray protection standards, Radiology 22:739 (1934).
8. Glocker, R. and E. Kaupp, Uber den Strahlenschutz und die Toleranzdosis, Strahlentherapie 20:144–152 (1935).
9. Sievert, F. M., Einige Untersuchungen uber Vorrichtungen zum Schutz gegen Rontgenstrahlen, Acta Radiol, 4:61–75 (1925).
10. Barclay, A. S. and S. Cox, The radiation risks of the roentgenologist, Am. J. Roentgenol. 19:551 (1928).
11. Failla, G., Radium protection, Radiology 19:12–21 (1932).
12. Kaye, G. W. C., Roentgenology. Its Early History. Some Basic Principles and Protection Measures, Paul B. Hoeber Inc., N. Y.

13. Advisory Committee on X-Ray and Radium Protection, X-ray Protection, Bureau Standards Handbook 15 1931.

14. Taylor, L. S., X-ray protection, J. Am. Med. Soc. 116:136–140 (1941).

15. Wintz and Rump, League of Nations Pub. CH-1054 (1931).

16. X-Ray Protection, Nat. Bureau Standards Handbook HB-20, 1936; Radium Protection, Nat. Bureau Standards Handbook H-23, 1938.

17. McClelland, W. R., Health Hazards in the Production and Handling of Radium, Dept. of Mines, Canada, Ore Dressing and Metallurgical Investigation No. 550.

18. Schlundt, H., W. McGarock, and M. Brown, Dangers in refining radioactive substances, J. Ind. Hyg. 13:117–133 (1931).

19. Peller, S., Lung cancer among mine workers in joachimstahl, Human Biology 11:130–143 (1939).

20. Dohnert, H. R., Experimentelle Untersuchunger zur Frage des Schneeberger Lungenkresbses, Zeits, F. Krebsforschung, 47:209–239 (1938).

21. Evans, R. D., The Toxicity of Small Doses of Neutrons and Other Radiations, Unpublished.

22. Failla, G., Unpublished data.

23. Martland, H. S., Occurrence of malignancy in radioactive persons, Am. J. Cancer 15:2435–2516 (1931).

24. National Bureau of Standards Handbook H-27, 1941.

25. Lewis, Thomas, The Blood Vessels of the Human Skin and their Responses, Shaw and Sons, Ltd., London, 1926.

26. Larkin, John C., An erythematous skin reaction produced by an alpha-particle beam., Am. J. Roentgenol. 45:109 (1941).

27. Colwell, H. A. and S. Russ, X-Ray and Radium Injuries, Oxford Med. Pub., 1934.

28. Aebersold, P. C. and J. H. Lawrence, The physiological effects of neutron rays, Ann. Review of Physiology 4:35–48 (1942).

29. CH-2311.

30. Russ, S. and G. M. Scott, The biological effects of continuous gamma irradiation, with a note on protection, Brit. J. Radio. 10:619 (1937); ibid. 12:440 (1939).

31. Muller, H. J., Artificial transmutation of the gene, Science 66:84–87 (1927).

32. Little, C. E. and J. J. Bagg, The occurrence of two heritable types of abnormality among descendents of X-rayed mice, Am. J. Roentgenol. and Radium therapy 10:795 (1933).

33. Snell, G. D. and F. D. Ames, Hereditary changes in the descendents of female mice exposed to roentgen rays, Am. J. Roentgenol and Radium Therapy 41: 248–255 (1939); The induction by irradiation with neutrons of hereditary changes in mice, Proc. Nat. Acad. Science, Washington 25:11–16 (1939); The production of translocations and mutations in mice by means of X rays, Am. Naturalist 68:178 (1934).

34. Mottram, J. C., Proc. Royal Soc. Med. 35:171–722 (1942).

35. CH-946.

36. Taylor, L. S., Roentgen Ray Protection, Science of Radiology, Chapter XIXX, pp 332–343, 1933.

37. Taylor, L. S., The work of the national and international committees on X-ray and Radium Protection Radiology 19: 1–4 (1932).

38. McWhirter, R., Radiosensitivity in relations to the time intensity factor, Radiology 9:287–299 (1936).